LINEAR NETWORK REPRESENTATION OF MULTISTATE MODELS OF TRANSPORT

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ABSTRACT By introducing external driving forces in rate-theory models of transport we show how the Eyring rate equations can be transformed into Ohm's law with potentials that obey Kirchhoff's second law. From such a formalism the state diagram of a multioccupancy multicomponent system can be directly converted into a linear network with resistors connecting nodal (branch) points and with capacitances connecting each nodal point with a reference point. The external forces appear as emf or current generators in the network. This theory allows the algebraic methods of linear network theory to be used in solving the flux equations for multistate models and is particularly useful for making proper simplifying approximations in models of complex membrane structure. Some general properties of linear network representation are also deduced. It is shown, for instance, that Maxwell's reciprocity relationships of linear networks lead directly to Onsager's relationships in the near equilibrium region. Finally, as an example of the procedure, the equivalent circuit method is used to solve the equations for a few transport models.

INTRODUCTION

Linear network theory has been introduced in thermodynamic treatments of membrane phenomena in order to facilitate the description of the kinetic properties of systems in which chemical reactions and transport processes take place (Oster et al., 1973). The algebraic tools of linear network theory were thus made available for solving more complex phenomena of active and coupled transport of particles through membranes (Schnakenberg, 1977; Mikulecky et al., 1977; Mikulecky, 1979).

The resistive elements in network thermodynamics are generally defined from relationships between local thermodynamic forces and fluxes (Wyatt, 1978). More recently, however, it has been shown that the conductance of multioccupancy channels can be represented by equivalent circuits[1] where the resistive elements are associated with the energy of the occupancy configurations and not directly derived from the local flows and driving forces. On the other hand, the equivalent circuits in these cases were only derived for particular models. This raises the question about the extent to which such a linear network can represent a model of arbitrary complexity. A more general development of this approach has therefore been carried out and will be presented in this paper.

The starting point is the Eyring rate formulation, which describes the transport of particles through a membrane that consists of a sequence of barriers and sites. The equations in this formulation are linear with respect to the state variables (probability of occurrence of the different states), and hence various techniques of linear algebra can be used to solve the equations.

A convenient way to represent the rate equations is with a state diagram where all states are written down in a two-dimensional array and connected with lines that indicate the possible transitions between states. This was used by Heckmann (1965*a*, *b*) in studying the properties of systems exhibiting single-file diffusion and has since become a standard procedure (cf. Hille and Schwarz, 1978). For simpler cases the system of linear equations (master equations), derived from the state diagram, can be solved by straightforward algebraic manipulations (Heckmann, 1965*a*,*b*; Chizmadjev and Aytian, 1977). For systems with numerous states, however, the equations have been solved either by numerical methods (i.e., matrix inversion[2]) or by the method of partial diagrams (Hill, 1966, 1977; King and Altmann, 1956; Hille and Schwarz, 1978).

The usefulness of constructing a linear network from a state diagram comes from taking advantage of the properties of closed loops that appear in the state diagram. These properties can be expressed in terms of loop equations that relate the products of forward and backward jump frequencies (formed around closed loops) to the externally applied forces. With the use of such loop equations the system of rate equations represented by a state diagram can be transformed into a linear network with resistive

[1]Sandblom, J., G. Eisenman, and J. Hägglund. Multioccupancy models of single-filing channels. Properties of a four-site model with three barriers separating the sites. Manuscript submitted for publication.

[2]Hägglund, J., G. Eisenman, and J. Sandblom. Single salt behaviour or a four-site single filing channel with barriers at its middle and ends. Manuscript submitted for publication.

elements connecting nodal points and with batteries inserted in the loops. This type of representation lends itself more readily to network calculations than the straightforward application of network thermodynamics which models the nonlinear rate equations with nonlinear conductive elements such as transistors (Wyatt, 1978).

THEORY

Rate Equations

We consider the system to be a membrane channel containing any number of components in a finite number of possible configurations (states), two of which are shown in Fig. 1. The probability of occurrence of states I and J are given the symbols Q_i, Q_j to emphasize that concentration in the thermodynamic system is represented by charge in the electrical network. If the transition between I and J involves the transfer of particles from one state to another, the flow J_{ij} from state I to state J is given by the Eyring rate theory.

$$J_{ij} = Q_i k_{ij} \exp\left(-\sum_k f_{ij}^k z_k FE/RT\right) - Q_j k_{ji} \exp\left(-\sum_k f_{ji}^k z_k FE/RT\right), \quad (1)$$

where k_{ij}, k_{ji} are the rate constants and E the membrane potential (the left side of the membrane being taken as reference). The quantities f_{ij}^k and f_{ji}^k are defined as the fractions of the total membrane potential that lie between the equilibrium and activated positions of species k in the transition between states I and J. This implies that the fractions f_{ij}^k corresponding to particles not involved in the transition I-J are set equal to zero.

The quantity f_{ji}^k, which is associated with a direction opposite to that associated with f_{ij}^k, is defined with a sign opposite to that of f_{ij}^k (and is the reason why both exponential terms in Eq. 1 contain a minus sign). By assigning directional signs to the quantities f_{ij}^k, f_{ji}^k they acquire a property essential to the theory; namely, that if the sum of $(f_{ij}^k - f_{ji}^k)$ is formed around a closed loop in the state diagram it assumes a value that is either zero or an integer. The reason for this is that a path which constitutes a closed loop through the state diagram describes either the passage of one or more ions through the entire channel (thus moving through the total membrane potential) or it describes an excursion from a state with a return to the same state without having produced a net displacement of any ions. We can express this important property of a state diagram by the following relationship

$$\sum_{\substack{i,j \\ o}} (f_{ij}^k - f_{ji}^k) = m_k$$

$$m_k = \ldots -2, -1, 0, 1, 2, \ldots, \quad (2)$$

where each loop has a specified integer (or zero) value of m_k.

There is also a restriction on the rate constants (k), which must satisfy the condition of microscopic reversibility. This adds a set of equations that are most conveniently expressed with the aid of closed loops in the state diagram. According to the principle of microscopic reversibility (detailed balance; Hill, 1977) the product of rate constants in one direction around a loop is equal to the product of rate constants in the other direction, or

$$\prod_{\substack{i,j \\ o}} \frac{k_{ij}}{k_{ji}} = 1. \quad (3)$$

Eq. 1 describes only the transfer of particles between two adjacent sites within the channel and does not include the case where transitions occur between a site and the solution (i.e., across the outer barriers facing the external solutions). Therefore it does not contain the explicit dependence on external solution concentrations. Adding equations for the flow of particles across the outer barriers, however, introduces the concentrations explicitly into the system of equations, for instance for a jump from the left solution

$$J_{ij} = a_k' Q_i k_{ij} \exp\left(-\sum_k f_{ij}^k z_k FE/RT\right) - Q_j k_{ji} \exp\left(-\sum_k f_{ji}^k z_k FE/RT\right)$$

where a_k' is the activity of species k in the left-side solution.

This activity term will be replaced by a product of activities if we allow for multiparticle jumps, and we will maintain this generality below. To add the concentration-dependent rate equations for the outer barriers to the system of flux equations, while retaining the form of Eq. 1, we will express the concentrations (activities) in exponential form. For this purpose we define a set of quantities h_{ij}^k.

$$h_{ij}^k \begin{cases} = (RT/z_k FE_k) \ln a_k' & \text{if transition } I\text{-}J \text{ involves jump of particles k from left solution;} \\ = (RT/z_k FE_k) \ln a_k'' & \text{if transition } I\text{-}J \text{ involves jump of particles k from right solution;} \\ = 0 & \text{otherwise.} \end{cases} \quad (4)$$

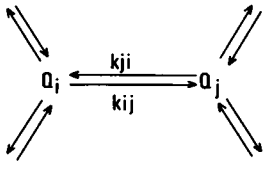

FIGURE 1 The transition between two states I and J are indicated by arrows. The state variables are labeled Q_i, Q_j, respectively, and k_{ij}, k_{ji} denote the forward and backward rate constants (see text).

E_k is the equilibrium potential of component k, defined as

$$E_k = (RT/z_kF)\ln a_k'/a_k'' \tag{5}$$

where $'$ refers to the left side and $''$ to the right side of the membrane. With the use of h_{ij}^k, h_{ji}^k we now write the flux equations as

$$J_{ij} = Q_i k_{ij} \exp\left[-\sum_k (z_kF/RT)(f_{ij}^k E - h_{ij}^k E_k)\right] - Q_j k_{ji} \exp\left[-\sum_k (z_kF/RT)(f_{ji}^k E - h_{ji}^k E_k)\right] \tag{6}$$

and by the summation we have included the possibility for multiparticle jumps. With the given definition, the quantities of h_{ij}^k will satisfy the same summation rule as do the f_{ij}^k if the summations are carried out through closed loops, since

$$\sum_{i,j}{}_{o} (h_{ij}^k - h_{ji}^k) = m_k(RT/z_kFE_k)\ln a_k' - m_k(RT/z_kFE_k)\ln a_k'' = m_k$$
$$m_k = -2, -1, 0, 1. \tag{7}$$

By writing the concentrations (activities) as exponential factors, the flux equations assume a unified form for all possible transitions in the system. The notations may be still further simplified, however, by giving a symbol to the sum of the electrical and chemical parts of the exponents in Eq. 6.

$$e_{ij}^k = -(z_kF/RT)(f_{ij}^k E - h_{ij}^k E_k) \tag{8}$$

and by applying the summation rules for f_{ij}^k, h_{ij}^k we get a relationship between the electrochemical potentials e_{ij}^k and the total electrochemical potential difference across the membrane, $\bar{E}_k$, which we define as

$$\bar{E}_k = (E - E_k)z_kF/RT. \tag{9}$$

Combining Eqs. 2, 7, and 8 gives for the summation of $(e_{ij}^k - e_{ji}^k)$ around closed loops:

$$\sum_{i,j}{}_{o} (e_{ij}^k - e_{ji}^k) = -(z_kF/RT) \cdot \left[\sum_{i,j}{}_{o} (f_{ij}^k - f_{ji}^k)E - \sum_{i,j}{}_{o} (h_{ij}^k - h_{ji}^k)E_k\right] = -m_k\bar{E}_k. \tag{10}$$

With the quantities e_{ji}^k the flux Eqs. 6 can be written as

$$J_{ij} = Q_i k_{ij} \exp \sum_k e_{ij}^k - Q_j k_{ji} \exp \sum_k e_{ji}^k, \tag{11}$$

and this expression forms the basis for developing the circuit representation because the loop properties of the rate constants (Eq. 3) and the electrochemical potentials e_{ij}^k (Eq. 10) can be comprised into loop equations.

Loop Equations

If we perform a summation over the index k in Eq. 10 and then raise both sides to an exponent, we can combine Eqs. 3 and 10 into a single loop equation to be used in constructing the equivalent circuit of the state diagram

$$\prod_{i,j}{}_{o} \frac{k_{ij} \exp \sum_k e_{ij}^k}{k_{ji} \exp \sum_k e_{ji}^k} = \exp - \sum_k m_k\bar{E}_k. \tag{12}$$

In deriving Eq. 7 and hence Eqs. 10 and 12 we have implicitly assumed that the particles do not combine in the membrane to produce different chemical species. We can take such combinations into account, however, by introducing the affinities of the reactants that will add the term $-\Sigma_i(n_i'A_i' + n_i''A_i'')$ to the exponential terms in Eq. 12 where A_i' and A_i'' are the left- and right-side affinities

$$A_i = -\sum_k \nu_{ik}\mu_k.$$

Although the theory applies to coupled reaction-diffusion flows we will restrict the following treatment and applications to pure barrier-type diffusion.

Node Equations

Two more relationships complete the theoretical description of material transport through the channel. The first is the mass balance equation which applies to all states and is written for each branch (nodal) point in the state diagram,

$$\sum_j J_{ij} = -\frac{dQ_i}{dt}. \tag{13}$$

The right-hand side of Eq. 13 is zero at steady state. Eq. 13 corresponds to Kirchhoff's current law in linear network theory (Schnakenberg, 1977). Inserting the fluxes from Eq. 11 in Eq. 13 yields the master equation, which constitutes a set of linear equations in terms of the state variables, Q_i.

The complete set of equations are not linearly independent, however, and the additional relationship needed to define the system is given by the sum of all Q_i (defined as probabilities) which must be equal to unity

$$\sum_i Q_i = 1. \tag{14}$$

Now, to represent the system, which is completely described by Eqs. 10–14, by a resistive network, it is necessary to convert the flux Eqs. 11 into the form of Ohm's law, where the potentials are defined so that they will obey Kirchhoff's second law.

Linear Network Elements

In this section we will describe the series of steps by which this is accomplished, namely a transformation of Eq. 11 into the following form,

$$J_{ij} = g_{ij}(U_i - U_j), \tag{15}$$

where U_i and U_j must be state functions, i.e., functions that depend only on the properties of the corresponding states. To accomplish this we write Eq. 11 in the form

$$J_{ij} = g_{ij}U_i - g_{ji}U_j, \tag{16}$$

and denote the ratios between Q_i and U_i and between Q_j and U_j by capacitances.

$$C(i) = Q_i/U_i \tag{17a}$$

$$C(j) = Q_j/U_j. \tag{17b}$$

The conductances g_{ij} and g_{ji} are therefore defined as follows:

$$g_{ij} = C(i)k_{ij} \exp \sum_k e_{ij}^k \tag{18a}$$

and

$$g_{ji} = C(j)k_{ji} \exp \sum_k e_{ji}^k. \tag{18b}$$

It is seen from these definitions that the conductances will be equal and consequently that Eq. 15 will be satisfied if the following relationship is obeyed

$$C(i)\frac{k_{ij} \exp \sum_k e_{ij}^k}{k_{ji} \exp \sum_k e_{ji}^k} = C(j) \tag{19}$$

Although the capacitance function has been introduced as an arbitrary function, the fact that it must be a state function (according to Eq. 17), taken together with Eq. 19, is sufficient to define the capacitances uniquely.

If we first introduce one of the capacitances $C(0)$ as a reference, we can use Eq. 19 successively along a path from states 0 to I to eliminate the intermediate states and get an expression for $C(i)$:

$$C(i) = C(0)\prod_{\substack{l,m \\ 0\to I}} \frac{k_{lm} \exp \sum_k e_{lm}^k}{k_{ml} \exp \sum_k e_{ml}^k}. \tag{20}$$

Since the value of $C(0)$ can be given an arbitrary value it is henceforth set equal to unity. We now have to define the conditions for which $C(i)$ (and therefore U_i) is a state function: i.e., to find the conditions for its being independent of how the path from 0 to I is chosen. This, as will be seen, will impose restrictions on the choice of paths.

State Function $C(i)$

We will examine the behavior of the product in Eq. 20 for different paths connecting states 0 and I. The product is seen to consist of a ratio that corresponds to forward and reverse rates along a particular path and thus the product in Eq. 20 does not receive any contribution if we move forward and backward along the same track and thereby multiply two quantities which are the inverse of each other. We can therefore generate the product for any path connecting states 0 and I from the product of any other path connecting states 0 and I by multiplying by the product of a closed loop (see Fig. 2).

Hence we write, with reference to Fig. 2,

$$\prod_2 = \prod_1 \cdot \prod_o,$$

where the symbols refer to the products of Eq. 20 along the indicated paths. According to Eq. 12, however, the product around a closed loop is equal to $\exp - \Sigma_k m_k \bar{E}_k$ and we have reduced the problem to finding the conditions when

$$\prod_o = 1,$$

i.e., when m_k can be set equal to zero. The products along arbitrary chosen paths starting from $C(0)$ will therefore be equal, depending only on the endpoint, and thereby define a state function.

Dividing Barrier

From previous arguments it is clear that m_k is zero for loops that do not correspond to a net displacement from one aqueous solution to another of a particle of species k. If we therefore choose an arbitrary barrier as a divider in the state diagram, it follows that m_k will be zero if, in forming loops, we exclude transitions across this barrier.

Furthermore, since any state can be connected with the reference state along paths that do not cross the divider (i.e., we can load the system from the two sides of the membrane) we define the state function $C(i)$ from Eq. 20 where the product is taken along paths that do not include transitions across the dividing barrier.

Since, by definition, Eq. 19 is satisfied everywhere along such paths, it follows that Eq. 15 will be satisfied for all transitions that do not take place across the dividing

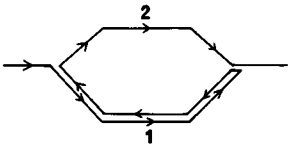

FIGURE 2 Two different pathways with the same end point are shown, where the upper path is obtained from the lower path by forming a closed loop.

barrier. On the other hand, if I-J represents a transition across the dividing barrier, Eq. 15 will no longer hold, because the product

$$\prod_{0\to J} = \prod_{0\to I} \cdot \prod_{I\to J}$$

$$= C(i) \cdot (k_{ij} \exp \sum_k e_{ij}^k / k_{ji} \exp \sum_k e_{ji}^k) \quad (21)$$

extends from 0 to J across the divider and is therefore not equal to $C(j)$. The product of Eq. 21 can be generated from the path that defines $C(j)$ (i.e., that does not cross the divider), however, by adding a loop that goes back from state J through 0 and then follows the path defined by Eq. 21. This loop crosses the dividing barrier once and must therefore express a net displacement of a number of particles through the membrane, namely the same number that cross the dividing barrier in the transition from I to J and that we label n_k.

For transitions that take place across the dividing barrier we replace Eq. 19 with

$$C(i) \cdot (k_{ij} \exp \sum_k e_{ij}^k / k_{ji} \exp \sum_k e_{ji}^k) = C(j) \cdot \prod_\circ$$

$$= C(j) \exp - \sum_k n_k \bar{E}_k,$$

where n_k is equal to the number of particles of species k, that simultaneously jump across the dividing barrier in the transition from I to J. From this it also follows by the definitions of g_{ij}, g_{ji} (Eq. 18) that

$$g_{ij} = g_{ji} \exp - \sum_k n_k \bar{E}_k \quad (22)$$

for transitions taking place across the dividing barrier.

To introduce Eq. 22 in Eq. 16 we rearrange the latter in a few alternative ways

$$J_{ij} = g_{ij}(U_i - U_j) + U_j(g_{ij} - g_{ji}) \quad (23a)$$

$$= g_{ji}(U_i - U_j) + U_i(g_{ij} - g_{ji}) \quad (23b)$$

$$= \frac{g_{ji} + g_{ij}}{2}(U_i - U_j) + \frac{U_i + U_j}{2}(g_{ij} - g_{ij}). \quad (23c)$$

The term $(g_{ij} - g_{ji})$ can then be expressed in terms of the corresponding conductance and of the external forces by taking into account Eq. 22

$$g_{ij} - g_{ji} = g_{ij}\left(1 - \exp \sum_k n_k \bar{E}_k\right) = \quad (24a)$$

$$= g_{ji}\left[\exp - \left(\sum_k n_k \bar{E}_k\right) - 1\right] = \quad (24b)$$

$$= (g_{ij} + g_{ji}) \operatorname{tgh} - \frac{1}{2} \sum_k n_k \bar{E}_k. \quad (24c)$$

The transitions across the dividing barrier are therefore seen to introduce source terms which are equivalent to emf or current generators.

It is seen from Eq. 23, however, that these source terms are directly proportional to the potentials of the source terminals. In the general case it is therefore necessary to solve the source terminal potentials and thereby take into account Eq. 14, the equation describing the conservation of charge in the system.

Using the definition of network potentials, Eq. 17, we can rewrite Eq. 14 as

$$\sum_i U_i C(i) = 1, \quad (25)$$

which is seen to contain explicitly all of the node potentials of the system. As will be shown below, however, simple circuit methods reduce the problem to that of solving only the potentials for the source terms appearing in Eq. 23. The circuit method therefore minimizes the number of independent variables to be solved, in comparison with conventional methods that generally require a solution of all the node potentials (cf. Hill, 1966). The advantage of the circuit method becomes even more apparent when the potentials are nearly equal (i.e., near equilibrium or when the dividing barrier is very large compared with the other barriers). In this case we get from Eq. 25

$$U_i^0 = 1/\sum_i C(i), \quad (26)$$

where U_i^0 is the value of the potentials at equilibrium. Combining this result with Eqs. 23 and 24 (Eqs. 23c and 24c, for instance), gives

$$J_{ij} = \frac{g_{ij} + g_{ji}}{2}(U_i - U_j + E_{ij}),$$

where the value of the emf, E_{ij} is given by

$$E_{ij} = \frac{2 \operatorname{tgh} - \frac{1}{2}\sum_k n_k \bar{E}_k}{\sum_i C(i)}. \quad (27)$$

In cases when Eq. 27 is valid, the network theory offers great advantages over other methods, because it eliminates the need to solve the potential differences in order to obtain the currents. Network methods will then often provide extreme shortcuts to the solutions as will be shown in a few examples given below.

Construction of a Linear Network from the State Diagram

The relationships developed in previous sections allow a linear network to be constructed from the state diagram by making an arbitrary choice of dividing barrier. All states

in the state diagram will represent nodal or branching points, each being connected to a reference state (ground state) by a capacitor with a capacitance given by Eq. 20.

Each connection between two states in the diagram (not involving the dividing barrier) is replaced by a resistor with a conductance value which is given by Eq. 18. For a conductance that represents a dividing peak, either one of the two ways of approaching the peak of their averaged value can be used as a conductance value (see Eq. 23).

The source terms are added as emf or current sources in the branches corresponding to the dividing barrier and the choice of source terms (Eq. 23) will determine the value of the corresponding conductances according to Eq. 23.

Near equilibrium the source terms can be simulated by batteries with emf given by Eq. 27 (see Fig. 3 *a*). For significant potential differences each source term becomes state dependent according to Eq. 23. This can be simulated by two amplifiers (See Fig. 3 *b*), a useful representation for simulation purposes. It is easily verified that each of the amplifier circuits satisfies Eq. 16 (the input resistance to each amplifier is assumed to be infinite).

All properties of the system are now incorporated in the topology of the network and in the equations for the network elements, the capacitances (Eq. 20), the conductances (Eq. 18) and the source terms (Eq. 23). Once the network has been constructed it is readily simulated by computer algorithms like NET or SPICE,[3] which allow the properties of the system to be studied in a convenient way.

The additional equations needed for this, however, are the connections between the network currents and the net flow of species through the membrane. In the steady state the net flow of particles is the same over every barrier as long as they do not combine to form different chemical species. If we then write the net flow of species across the dividing barrier we get for species k

$$J_k = \sum_{\substack{i,j \\ \text{dividing} \\ \text{barrier}}} n_k(ij)\, J_{ij} \tag{28}$$

where the summation is carried out over all transitions across the dividing barrier and where $n_k(ij)$ is the number of particles of species k that jump across the dividing barrier in the I-J transition.

If we allow chemical reactions to take place in the membrane it is appropriate to choose either one of the outer barriers as diffusion divider. This means that all loops that cross a reaction divider, but not the diffusion divider, will add a term to the exponent of the loop equation which is proportional to a reaction affinity on the side opposite that of the dividing barrier. This is analogous to a choice of conjugated flows and forces in a coupled diffusion reaction system (cf. Katchalsky and Curran, 1965).

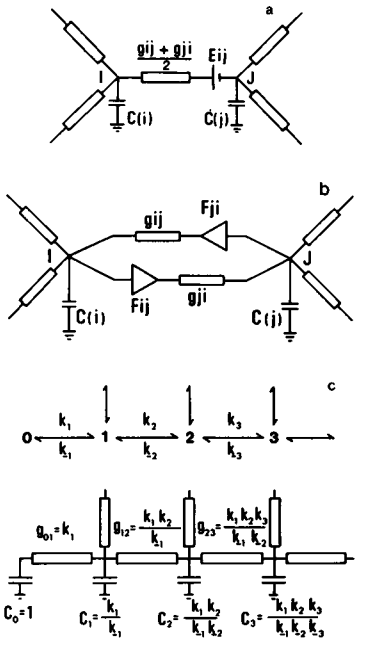

FIGURE 3 (*a*) Equivalent circuit representation of a part of a state diagram. The transition I-J is chosen to be a divider and the source term is represented by a battery with an emf obtained from Eq. 24c. (*b*) Same as in Fig. 3 *a* but with the source term represented by two amplifiers. To satisfy Eq. 16 the amplifications F_{ij} and F_{ji} are given by $F_{ij} = g_{ij}/g_{ji} = \exp -\Sigma_k n_k \bar{E}_k$ and $F_{ji} = g_{ji}/g_{ij} = \exp \Sigma_k n_k \bar{E}_k$, respectively. (*c*) Relationship between state diagram (*top*) and circuit elements (*bottom*). The jump rates ($= k_{ij} \exp \Sigma_k e^k_{ij}$) are labeled k for brevity in the upper part, and the circuit parameters derived from these jump rates are given in the lower part of the figure.

Finally the total membrane current is given by the sum of the conduction and displacement currents

$$I = \sum_k z_k \frac{J'_k + J''_k}{2} + \epsilon A \frac{dE}{dt}, \tag{29}$$

where E is the electric field and A the membrane area. This equation also follows from the fact that the inflow of current on one side is the same as the outflow of current on the other side, or

$$I = \sum_k z_k J'_k + A \frac{d\sigma'}{dt} = \sum_k z_k J''_k - A \frac{d\sigma''}{dt} \tag{30}$$

where σ', σ'' are the surface charge densities on the two sides of the membrane. With

$$\epsilon E = \frac{\sigma' - \sigma''}{2}$$

Eq. 29 is derived from Eq. 30.

[3]Versions of SPICE compatible with most general purpose computers are available free of charge. For details, write to Prof. D. O. Pederson, Dept. of EECS, University of California at Berkeley, Berkeley, California. Prof. Pederson is one of the authors of SPICE.

Relationships between Network Elements, Rate Constants and Energy Parameters

Eqs. 18 and 20 for the relationships between rate constants and circuit parameters provide simple rules for translating back and forth between the two sets of parameters. Since the term $\exp \Sigma_k e_{ij}^k$ is a notation for the concentration and voltage-dependent part of the rate constants we can regard the terms in the products of Eqs. 18 and 20 as forward and backward jump frequencies. The circuit parameters are therefore obtained from ratios between forward and backward jump frequencies along paths which do not cross the dividing barrier, as exemplified in Fig. 3 *c*, a procedure that resembles the use of partial diagrams in the King-Altmann theory (King and Altman, 1956).

The network elements can also be related to the energy parameters of the system. If we denote the concentration and voltage-independent part of the capacitance function by $C^0(i)$ we get from Eq. 20

$$C^0(i) = \prod_{\substack{l,m \\ 0 \to I}} \frac{k_{lm}}{k_{ml}} = \frac{v_n \exp - \sum_{l,m} \frac{\Delta G^*_{lm}}{RT}}{\exp - \sum_{l,m} \frac{\Delta G^*_{ml}}{RT}}$$

$$= v^n \exp - \sum_{\substack{l,m \\ 0 \to I}} \frac{\Delta G^*_{lm} - \Delta G^*_{ml}}{RT}$$

$$= v^n \exp - \frac{\Delta G_i}{RT} = v^n K_i \qquad (31)$$

where v is a constant (in Molar^{-1}) (see Läuger, 1973) and n is the occupancy number of state I. ΔG^*_{lm} and ΔG^*_{ml} are the activation energies of the forward and backward transitions and the difference $(\Delta G^*_{lm} - \Delta G^*_{ml})$ is the equilibrium free energy difference between states L and M.

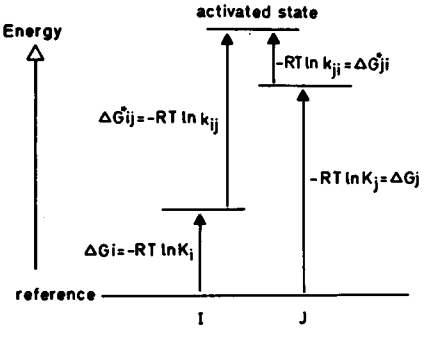

FIGURE 4 The figure shows the energy levels of a channel in states I and J. $-RT \ln K_i$ is the total energy required to bring the number of ions from a reference state (usually the empty state) into the channel in configuration I. $-RT \ln K_j$ is the corresponding energy for configuration J. $-RT \ln k_{ij}$ and $-RT \ln k_{ji}$ are the activation energies (apart from a constant) for the transitions $I \to J$ and $J \to I$, respectively. The total energy of the activated state (the peak energy) $-RT \ln P_{ij} = -RT \ln P_{ji}$ is consequently equal to the sum of the partial energies, or $-RT \ln K_i k_{ij} = -RT \ln K_j k_{ji}$.

The summation is carried over all steps L-M lying on the chosen path between 0 and I and the sum is therefore equal to ΔG_i, the equilibrium free energy difference between states 0 and I. $C^0(i)$ is therefore seen in Eq. 31 to be proportional to the equilibrium constant K_i of the transition between states 0 and I $(0 \leftrightarrow I)$, where state 0 is a reference state.

Similar arguments apply to the conductances where the voltage and concentration-independent part is given by

$$g^0_{ij} = C^0(i) k_{ij} = v^n \exp - \frac{\Delta G_i + \Delta G^*_{ij}}{RT} = P_{ij} = P_{ji}. \qquad (32)$$

The energy in this case consists of an equilibrium part (ΔG_i) and an activation part (ΔG^*_{ij}) and may be viewed as the net energy to reach the configuration in the activated state from the reference state 0, and the exponent of this parameter (the P parameter) consequently has the meaning of a permeability. The relationship between binding constants and permeabilities are shown in Fig. 4 in terms of equilibrium and activated energy levels of the system.[4]

If experimental data are interpreted in terms of a particular state diagram model it is possible to extract the values of $C^0(i)$ and g^0_{ij}. The individual rate constants are then obtained from the corresponding ratios (see Eq. 32 and Fig. 4).

$$k_{ij} = \frac{P_{ij}}{K_i} = \frac{g^0_{ij}}{C^0(i)} \qquad (33a)$$

$$k_{ji} = \frac{P_{ji}}{K_j} = \frac{g^0_{ji}}{C^0(j)}. \qquad (33b)$$

The capacitance function can also be given a physical interpretation which is independent of the state diagram. If we imagine that the resistance of the dividing barrier becomes infinite without changing anything else in the system, including the applied forces and the distribution of the electric field, the system will come to equilibrium and all potentials become equal, i.e., $U^0_i = U^0_0$. We therefore get, by definition,

$$U^0_i = \frac{Q^0_i}{C(i)} = Q^0_0 = \frac{1}{\sum_i C(i)}, \qquad (34)$$

since the value of $C(i)$ is not affected by the assumption of an infinite dividing barrier. The capacitance $C(i)$ is, therefore, given by

$$C(i) = \frac{Q^0_i}{Q^0_0} \qquad (35)$$

[4]Läuger (1973) in his treatment of single-ion-occupied pores introduced quantities R_i and S_i, which near equilibrium correspond to our K and P parameters. The relationships between his and our notations are $K_i = \overline{R}_i$, $P_{ij}/P_{ik} = \overline{S}_{ik}/\overline{S}_{ij}$.

and expresses the equilibrium binding to the empty membrane (assuming state 0 to be the empty state) given the applied forces and an imaginary "reflecting wall" at the site of the dividing barrier.

RESULTS

Linear Region Near Equilibrium (Onsager and Maxwell Reciprocity)

When all external forces in the system are set equal to zero, the system is at equilibrium and the potentials become equal. Each state variable Q_i is then a function only of the capacitances according to Eq. 17, i.e., they become independent of the peaks. This is a result which can be derived directly from equilibrium thermodynamics (Hille and Schwarz, 1978), but which we have shown here to be the algebraic result of defining the capacitance functions from the Eyring rate equations.

Another important result is that since the battery emf are directly proportional to the thermodynamic forces near equilibrium (see Eq. 27) the Onsager reciprocal relationships of irreversible thermodynamics can be derived from the Maxwell reciprocity relationships of linear network theory. The current I_i in branch (i) of a network containing resistors and batteries is given by a linear combination of all the emf (E_j), $I_i = \Sigma_j G_{ij} E_j$, where the coefficients G_{ij} are called transfer conductances. According to Maxwell's reciprocity theorem, the transfer conductances obey symmetry relationships, i.e., $G_{ij} = G_{ji}$. Since Onsager's theorem describes a similar symmetry for the linear laws of irreversible thermodynamics, and since we have identified forces and flows with emf and currents in the network, we have shown that the two theorems are equivalent near equilibrium.

Although this result is a natural consequence of having introduced the microscopic reversibility principle in the physical treatment, it nevertheless emphasizes the useful form given to the equations by the network representation. However, it is only near equilibrium that the batteries or current generators are an exact physical representation describing the energy dissipation in the system. More generally the source term representations must be viewed as a purely formal description of the system which is useful for algebraic calculations.

Circuit Reduction (Parameter Lumping)

The explicit solutions to the particle fluxes are more readily derived by taking advantage of circuit reduction methods. Through the use of such methods, it is possible to condense the equivalent circuits to a point where only nodes branching into circuit sources are left. The other nodes form stars that contain only resistive elements (neglecting capacitances in the steady state) and are therefore easily eliminated.

According to the star-mesh transformation theorem (Rosen, 1924), a node (star of branches ij, il, ik, etc.) can be replaced by a mesh of conductors joining every pair of the points jl, lk, jk, etc. (i being eliminated) without affecting the rest of the network, if the added conductances ($\bar{g}_{jl}$, $\bar{g}_{lk}$, $\bar{g}_k$, etc.) are related to those of the eliminated star (g_{ij}, g_{il}, g_{ik}, etc.) by

$$\bar{g}_{il} = \frac{g_{ij} g_{il}}{\sum_k g_{ik}}, \text{ etc.,} \tag{36}$$

where $\Sigma_k g_{ik}$ is the sum of all conductances of the eliminated star.

This transformation leads to a simpler circuit with lumped conductances ($\bar{g}$) which preserve the currents in the branches containing the sources. Unless we are dealing with the near equilibrium case, however, the transformation must also retain Eq. 25 for the transformed circuit. This can be done by applying Kirchhoff's current law (Eq. 13) to the eliminated nodes, which gives for the steady state

$$U_i = \frac{\sum_k g_{ik} U_k}{\sum_k g_{ik}}, \tag{37}$$

where g_{ik} is the conductance in branch ik, connecting node i with node k. Eq. 37 can be used to eliminate U_i from Eq. 25 in which case the capacitance $C(k)$ receives a contribution from $C(i)$ derived from Eq. 37.

$$\bar{C}(k) = C(k) + C(i) \cdot \frac{g_{ik}}{\sum_k g_{ik}}. \tag{38}$$

Eq. 25 is therefore preserved in the transformed circuit with a new set of lumped capacitors ($\bar{C}$). This reduction in the number of nodes can be performed successively to leave only the terminals of the current sources. Fig. 5 shows a reduced circuit comprising all systems which can be represented by a single source term. Such systems include the one-ion-occupied pore treated by Läuger (1973) or the three-barrier-two-ion occupied pores described in detail by Markin and Chizmadjev (1974), by

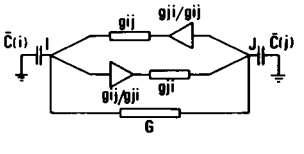

FIGURE 5 Reduced circuit of a system represented by a single source. $\bar{C}(i)$, $\bar{C}(j)$ are reduced capacitances and G the reduced conductance, in this case the total conductance of the system measured between the points I and J when the source branch is opened.

Hille and Schwarz (1978) and by Urban and Hladky (1979). Using the reduced circuit of Fig. 5 the solution to the current in terms of the external forces is now easily derived.

Single-Source Circuit

Ohm's law applied to the circuit of Fig. 5 gives immediately

$$J_{ij} = G(U_j - U_i) \tag{39}$$

and by combining this with Eqs. 16 and 25 we get the explicit solution for the current

$$J_{ij} = \frac{G(g_{ij} - g_{ji})}{\bar{C}(i)(g_{ji} + G) + \bar{C}(j)(g_{ij} + G)}. \tag{40}$$

The values of $\bar{C}(i)$, $\bar{C}(j)$ and G will depend on the topology of the original circuit as will be shown in the following examples.

Examples

In order to illustrate the procedures outlined in the paper and for comparison with other methods, a few specific examples applicable to a three-barrier two-site channel will be given with a detailed description of the steps involved.

The state diagram representing this system is shown in Fig. 6 *a*, where the arrows represent transitions (with rate constants k) between states of increasing occupancy (cf. Hille and Schwarz, 1978). If the central barrier is chosen to be the dividing barrier, the equivalent circuit is constructed from the state diagram by replacing all arrows by resistors, and by inserting a battery (or amplifiers) in the middle branch (which in this case corresponds to the central barrier).

Fig. 6 *b* shows the equivalent circuit constructed this way from the state diagram of Fig. 6 *a*. The values of the conductances in the circuit are functions of the external concentrations, of the applied voltage, and of the rate constants as described in the preceeding text. The explicit relationships are most easily derived by multiplying the rate constants along paths in the state diagram that do not cross the dividing barrier. All such paths will give the same result by virtue of the microscopic reversibility conditions and the summation properties.

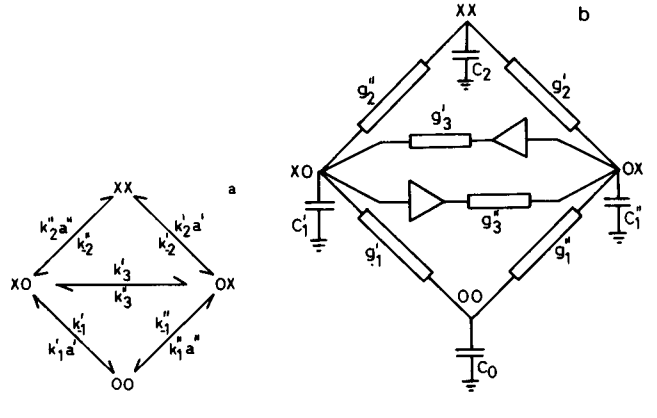

FIGURE 6 (*a*) State diagram of a three-barrier, two-site channel with a single component. The voltage-dependent parts of the forward and backward rates have been included in the rate constants for shortness of notations. (*b*) Equivalent circuit constructed from the state diagram of Fig. 6 *a*.

If we carry out such operations for the capacitances in Fig. 6 *b*, we get

$$C_0 = 1 \tag{41a}$$

$$C_1' = k_1'a'/k_{-1}' \qquad C_1'' = k_1''a''/k_{-1}'' \tag{41b}$$

$$C_2 = C_1'k_2''a''/k_{-2}'' = C_1''k_2'a'/k_{-2}' \tag{41c}$$

where a', a'' are the activities of the permeable ion on the two sides of the membrane. The rate constants (k) are voltage dependent according to the Eyring rate theory with exponents which depend on the distribution of the electric field.

Similar derivations for the conductances in Fig. 6 *b* give

$$g_1' = k_1'a' = C_1'k_{-1}' \qquad g_1'' = k_1''a'' = C_1''k_{-1}'' \tag{42a}$$

$$g_2' = C_1'k_2''a'' \qquad g_2'' = C_1''k_2'a' \tag{42b}$$

$$g_3' = C_1'k_3' \qquad g_3'' = C_1''k_3''. \tag{42c}$$

Steady State. The external conductance, i.e., the total conductance of the upper and lower branches in Fig. 6 *b*, is simply obtained from a parallel addition of the two branches

$$G = \frac{g_1'g_1''}{g_1' + g_1''} + \frac{g_2'g_2''}{g_2' + g_2''}. \tag{43}$$

The lumped capacitances $\bar{C}_1'$ and $\bar{C}_1''$ are derived using Eq. 38. This gives with reference to Fig. 6 *b*

$$\bar{C}_1' = C_1' + C_2\frac{g_2'}{g_2' + g_2''} + C_0\frac{g_1'}{g_1' + g_1''} \tag{43a}$$

$$\bar{C}_1'' = C_1'' + C_2\frac{g_2''}{g_2' + g_2''} + C_0\frac{g_1''}{g_1' + g_1''}. \tag{43b}$$

Inserting Eqs. 42 and 43 in Eq. 40 [putting $\bar{C}(i) = \bar{C}_1'$ and $\bar{C}(j) = \bar{C}_1''$] we get an expression for the current which becomes identical to that derived by Markin and Chizmadjev (1974) for equal concentrations (see Eq. 5.7) and more generally by Urban and Hladky (1979; Eq. 9), when the conductances and capacitances are substituted by the rate constants from Eqs. 41 and 42.

Undirectional Flux Ratio. A quantity frequently used to characterize single-filing transport is the

undirectional flux ratio. This ratio is related to the electrochemical potential difference across the membrane by an exponential relationship

$$\frac{\overrightarrow{J}}{\overleftarrow{J}} = \exp - nE \tag{44}$$

where the number n depends on the external solution concentrations as well as on the particular barrier profile.

If the fluxes across the membrane are measured by tracers it has been shown (Heckmann, 1965) that n can be related to the conductance or the permeability of the tracer.

Consider, for instance, the substance X and its tracer Y and define the conductance G_y of the tracer in the presence of X as

$$G_y = \left[\frac{I_y}{\bar{E}_y}\right]_{\bar{E}_x = 0}. \tag{45}$$

With this definition of G_y, the flux ratio exponent n is related to the equilibrium conductances G_y^0 and G_x^0 by the following relationship (Hodgkin and Keynes, 1955).

$$n = \frac{G_x^0}{G_y^0} \cdot \theta, \tag{46}$$

where θ is the ratio of the concentrations of Y and X. The inverse of n is called the correlation factor. With the use of Eq. 46 we can apply the equivalent circuit method in order to evaluate n. Since Y is a component separate from X we must proceed from the two-component state diagram of a three-barrier, two-site channel shown in Fig. 7 *a*. The corresponding equivalent circuit is shown in Fig. 7 *b* (since we are dealing exclusively with the steady state in this case we have omitted the capacitances from the circuit). In writing down the conductances in Fig. 7 *b* we have used the fact that, since Y is a tracer of X, the energy terms of Y are equal to those of X. Therefore the component Y does not change the conductance values, apart from the factor θ, the ratio between concentrations. In order to obtain an expression for G_y from the circuit of Fig. 7 *b*, we note that $\theta^2 \ll \theta \ll 1$. In setting $\bar{E}_x = 0$, the upper branches become effectively short circuited and the lower branches open circuited in view of this inequality, and the circuit now reduces to that of Fig. 7 *c*.

The batteries appearing in Fig. 7 *b* can be derived from Eq. 27 and since the system is near equilibrium we can write

$$E_x = \frac{-\bar{E}_x}{\sum C(i)}, \quad E_y = \frac{-\bar{E}_y}{\sum C(i)}.$$

The ratio between the conductances of X and Y is therefore directly obtained from the conductances in the circuits of Figs. 6 *b* and 7 *b* which gives for the value of n

$$n = \frac{G_x^0}{G_y^0} \cdot \theta = \left[\frac{1}{g_3} + \frac{\left(\frac{1}{g_1'} + \frac{1}{g_1''}\right)\left(\frac{1}{g_2'} + \frac{1}{g_2''}\right)}{\frac{1}{g_1'} + \frac{1}{g_1''} + \frac{1}{g_2'} + \frac{1}{g_2''}}\right]^{-1} \cdot \left[\frac{1}{g_3} + \frac{\frac{1}{g_1'}\left(\frac{1}{g_2''} + \frac{1}{g_2''}\right)}{\frac{1}{g_1'} + \frac{1}{g_2'} + \frac{1}{g_2''}} + \frac{\frac{1}{g_1''}\left(\frac{1}{g_2'} + \frac{1}{g_2''}\right)}{\frac{1}{g_1''} + \frac{1}{g_2'} + \frac{1}{g_2''}}\right]. \tag{47}$$

From this expression it is seen, for instance, that the value of n approaches 2 when g_3, g_2', and g_2'' are large, namely when the inner barrier is small and the external concentrations are high.

This derivation of Eq. 47 has demonstrated that the expression for n can be obtained from network theory with very few algebraic manipulations. Other methods require extensive calculations (Urban and Hladky, 1979; Levitt, 1978) although it is possible with a proper use of

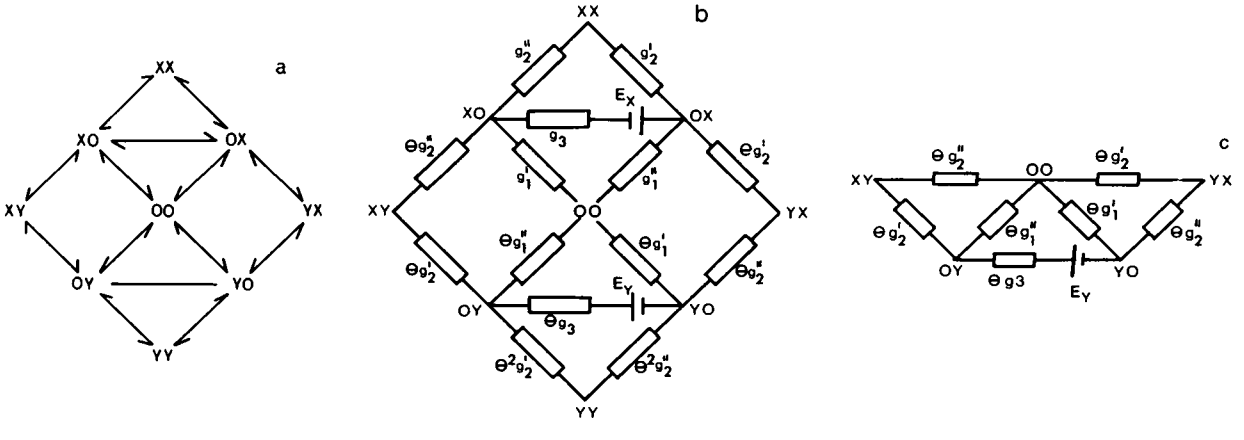

FIGURE 7 (*a*) State diagram of a three-barrier, three-site channel with two components. (*b*) Network representation of the state diagram of Fig. 7 *a* with the middle barrier taken as the dividing barrier. (*c*) Reduced network of Fig. 7 *b* when $E_x = 0$ and $\theta \ll 1$.

diagram-reducing methods to diminish the number of steps as discussed in the appendix of the paper by Hille and Schwarz (1978).

Step Response. In order to calculate the transient response to a step change in the applied electric field we will consider a very simple case and assume that the barrier profile is symmetric, the concentrations are equal on both sides and that the electric field lies entirely across the central barrier. With these assumptions it is only the conductance of the middle branch that will become voltage dependent and, due to symmetry, the sum of the potentials at the left and right nodal points will always remain constant. As a result of this the source term in Eq. 23c will be a constant following a step change in the applied electric field and the conductance g_3 will be given by (see Eq. 23c)

$$g_3 = \frac{g_3' + g_3''}{2} = C_1 \frac{k_3' + k_3''}{2} = a \cdot \frac{k_1}{k_{-1}} \cdot k_3 \cdot \cosh - \frac{zFE}{2RT}. \quad (48)$$

Also because of symmetry, the potentials at the upper and lower nodes will always remain constant and the circuit will behave like a balanced Wheatstone bridge. Since no current will pass through the upper and lower capacitances in this case the circuit can be rearranged to assume the form of Fig. 8.

The three time constants inherent in the circuit of Fig. 6 *b* are therefore equal (as a result of the assumptions) and the single time constant of the system is equal to the product of the total capacitance and the total resistance of the three branches in parallel (see Fig. 8).

$$\tau = \left[\left(\frac{1}{g_1'} + \frac{1}{g_1''}\right)^{-1} + \left(\frac{1}{g_2'} + \frac{1}{g_2''}\right)^{-1} + \frac{1}{g_3}\right]^{-1} \cdot \left[\frac{1}{C_1'} + \frac{1}{C_1''}\right]^{-1}. \quad (49)$$

Introducing Eqs. 42, 43 and 48 and taking the symmetry into account we can rewrite Eq. 49

$$\tau = \left[k_{-1} + k_3 \cosh - \frac{zFE}{2RT} + k_2 a\right]^{-1}, \quad (50)$$

where k_{-1}, k_2 and k_3 are now voltage independent.

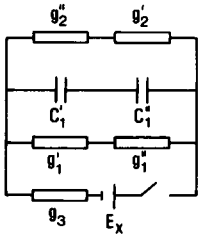

FIGURE 8 Same circuit as in Fig. 6 *b* with C_0 and C_2 omitted.

The time constant is seen to approach zero at high concentrations and it also has a bell-shaped dependence on the voltage, a behavior similar to that of a homogenous Nernst-Planck regime (Cole, 1965, Hägglund and Sandblom, 1972).

In view of the symmetry of the channel the currents flowing into and out of the membrane are the same and equal to the current flowing through the parallel network consisting of the two branches above and below the capacitances in Fig. 8.

The current in response to an electric field is therefore given by

$$J = (1 - \exp - t/\tau) J_\infty, \quad (51)$$

where J_∞ is the steady-state current obtained from Eq. 40; noting that as a result of symmetry $\bar{C}_1' = \bar{C}_1''$

$$J_\infty = \left[\frac{1}{g_3} + \frac{2}{g_1 + g_2}\right]^{-1} \left[1 + 2C_1 + C_2\right]^{-1} \cdot 2 \operatorname{tgh} - \frac{\bar{E}_x}{2}. \quad (52)$$

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